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## *Nature Cell Biology* Turning Point

The reward of great collaborations

Fiona M. Watt

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*Fiona Watt runs the Centre for Stem Cells and Regenerative Medicine at King's College London and is an outspoken advocate for women scientists. Since April 2018 she has been on secondment as Executive Chair of the Medical Research Council, one of the major funders of biomedical research in the UK.*

[886 words]

I did my postdoc at the Massachusetts Institute of Technology (MIT) with Howard Green, one of the pioneers of using cultured human keratinocytes as a treatment for burn victims. When I left MIT I established a research group at the Kennedy Institute of Rheumatology in London with a view to studying chondrocyte biology. As I had no prior experience in cartilage research, I started growing keratinocytes to test whether the new cell culture lab was running smoothly. I went on to publish a chondrocyte study describing a method for controlling chondrocyte shape, and thereby differentiation, in culture. This was inspired by Howard's observation that keratinocytes would undergo terminal differentiation if they were prevented from attaching to a culture substrate.

Although I was awarded tenure at the Kennedy I found it hard to abandon keratinocyte research and trying to stay abreast of two different research fields was making me unhappy. Looking for a change I was invited to apply for a job at the Imperial Cancer Research Fund (ICRF), a forerunner of the Francis Crick Institute. While interviewing there I met a fellow cell biologist, Charles O'Neill, who was also interested in cell shape. He described making petri dishes with patterns of circular palladium islands, each accommodating a single cell, and using them to examine the link between adhesion and anchorage-dependent growth in fibroblasts. We immediately struck up a collaboration and completed most of our experiments before I left the Kennedy Institute for the ICRF. We mainly communicated by letter - I still have one in which Charles summarised our findings of the previous month and ended 'Let's do another keratinocyte experiment with different times. Shall we see how we are situated in ten days (28<sup>th</sup> April).'

We submitted our paper to a highly respected journal but it was rejected on the grounds of lack of novelty. The decision letter was admirably straightforward: 'There is ... a two to one vote against publication...and my policy...is to accept the majority verdict'. The work was subsequently published in PNAS (Watt et al., 1988. Proc Natl Acad Sci U S A. 85:5576-5580), but I was deeply disappointed by that early rejection – 'anguished' best describes how I felt. Over the years I have received many rejection letters from different journals and I have come to realise that it is often our most innovative work that is rejected as 'lacking novelty'. Our 1988 paper showed that you could study stem cell-niche interactions at single cell resolution in a quantitative way by varying one environmental signal at a time, but it was another ten years before the use of micro-patterned islands to explore cell fate decisions began to take off (Chen et al., 1997. Science. 276:1425-1428).

Although my early work fostered a career-long interest in discovering the signals that control the switch from epidermal stem cells to differentiated cells, it wasn't until 2007 that I returned to micro-patterning. At the time I was working in Cambridge where I was introduced to Wilhelm Huck (now at the Radboud University in Nijmegen), a polymer chemist by training. We hit it off immediately – Willem establishing the basis of our collaboration as 'if you don't mess with the chemistry I won't mess with the biology'. When it was time to repeat the 1988 experiment the micro-patterning process was much simpler and we could quantitate differentiation much less subjectively than before. It was probably because of these advances that my postdoc, John Connelly (now a group leader at Queen Mary University of London), was genuinely surprised at how well the original experiment could be reproduced after twenty years. Our interest reignited, we used micro-patterned substrates to dissect how the extrinsic stimulus of restricted cell spreading was transduced into transcriptional responses to determine epidermal stem cell fate (Connelly et al., 2010. Nat Cell Biol. 12:711-718).

And what about 2018? We are still using micro-patterned substrates – and yes, the original experiment is still reproducible – but now we are examining the kinetics of differentiation in individual cells using live cell reporters. Our current collaborators – Ignacio Bordeu and Gunnar Pruessner from Imperial College London are mathematicians, who we met by chance through their collaborations with a neighbouring lab. Their computer simulations are not only helping us to understand the experimental data but also to generate new, testable hypotheses. We also have

the opportunity, as partners in the Human Cell Atlas initiative ([www.humancellatlas.org](http://www.humancellatlas.org)), to apply thirty years of in vitro observations to elucidating cell state transitions in human skin. Now our collaborators are the entire community of skin researchers worldwide.

So what are the lessons I have learnt in the past 30 years? First of all, patience – sometimes you have to put aside a problem until the technology catches up sufficiently to enable you to find a solution. Second, the power of interdisciplinary collaboration - my best have collaborations started through serendipity and flourished through common goals, mutual trust and affection. Third, persistence -- my message to scientists reading this who are suffering the anguish of a rejected paper is that you can always publish important work that others will find, read and cite regardless of the journal. That original 1988 paper has enriched my career, and I sometimes wonder how different my research path might have been if I hadn't met Charles all those years ago.